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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/028,396	HUYLEBROECK ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5 and 18-20* is/are pending in the application.

4a) Of the above claim(s) *7-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040618*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The amendment filed June 14, 2004 is acknowledged and has been entered. Claims 1 and 6 have been canceled. Claims 2-4 and 18 have been amended. Claims 19 and 20 have been added.

2. Claims 2-5 and 7-20 are pending in the application. Claims 7-17 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed November 10, 2003.

3. Claims 2-5 and 18-20 are currently under prosecution.

Information Disclosure Statement

4. The information disclosure filed June 14, 2004 has been considered. An initialed copy is enclosed.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment filed June 14, 2004 has obviated the grounds of objection and rejection set forth in the previous Office action mailed March 12, 2003.

Priority

6. Acknowledgment is made of Applicant's claim for foreign priority based on an application filed in Europe on June 25, 1999. It is noted, however, that applicant has

not filed a certified copy of the EPO 99202068.5 application as required by 35 U.S.C. 119(b).

Drawings

7. Receipt of the substitute drawing filed June 14, 2004 is acknowledged. The substitute drawing is acceptable.

Specification

8. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, sequences at page 2 (paragraph [0004]) of the specification (i.e., C-X_2-C-X_4-H-X_4-C and C-X_5-C-X_{12}-H-X_4-C) are not identified by sequence identification numbers.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Applicant is advised that the 37 CFR § 1.822 sets forth the symbols and format that should be used. Sequence identifiers for sequences appearing in the drawings may appear in the Brief Description of the Drawings. As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required.

Claim Objections

9. Claims 19 and 20 are objected to because the claims are drawn in the alternative to the subject matter of non-elected inventions.

Newly added claims 19 and 20 are drawn to "a process of identifying transcription factors [...] comprising: providing cells with a nucleic acid sequence comprising twice a SEQ ID NO: 1, separated by a spacer sequence N, wherein each SEQ ID NO: 1 may be sense or antisense, or the complement thereof, as bait for the screening of a library encoding potential transcription factors". SEQ ID NO: 1 is the nucleotide sequence, 5'-CACCT-3'; so, the complement thereof is the nucleotide sequence, 5'-AGGTG-3'. Accordingly, the claims are drawn to a process comprising providing cells having a nucleic acid molecule comprising a sequence selected from the group consisting of (a) CACCT-N-CACCT, (b) CACCT-N-AGGTG, (c) AGGTG-N-CACCT, and (d) AGGTG-N-AGGTG, where N can be a number of nucleotides ranging from 0 to at least 44, as set forth in the specification at page 6 (paragraph [0013]).

To the extent that the claims are drawn to a process comprising providing cells having a nucleic acid molecule comprising any one of these four distinct nucleotide sequences (i.e., (a), (b), (c), or (d)), the restriction set forth in the Office action mailed October 23, 2003 placed the claims in Groups I-IV; see page 2 of the Office action mailed October 23, 2003. In the response to this Office action filed November 10, 2003, Applicant elected the invention of Group I, claims 1-6, insofar as the claims are drawn to a process of comprising providing cells with a nucleic acid molecule comprising CACCT-N-CACCT. The Office action mailed March 12, 2004 made the restriction and election requirement FINAL and states that claims 1-6 were considered only to the extent of the elected invention. Therefore, newly added claims 19 and 20 encompass the subject matter of non-elected inventions and have been only been considered to the extent that the claims are drawn to the elected invention.

10. Claim 5 is objected to because of the following informality: The term "a4-integrin" should read, "α4-integrin". Appropriate correction is required.

11. Claim 18 is objected to because of the following informality: The comma after "wherein" is misplaced. The comma should be placed after "bait", so that the claim reads, "[...] wherein the at least twice a sequence is a first SEQ ID NO: 1 and a second SEQ ID NO: 1 separated by N as bait, wherein N is a spacer sequence". Appropriate correction is required. Additionally, it is suggested that "as bait" after "N" in the phrase be deleted, since this second recitation of the intended use is redundant.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reason set forth in section 16 of the Office action mailed March 12, 2004.

Claim 5 is drawn to a process of identifying transcription factors comprising providing cells with a nucleic acid sequence comprising two copies of the sequence "CACCT" separated by any number of nucleotides (i.e., "CACCT-N-CACCT"), wherein the nucleic acid sequence comprising two copies of the sequence "CACCT" separated by any number of nucleotides *originates from a promoter region* of a gene encoding the Brachyury, α4-integrin, follistatin, or E-cadherin.

DNA is a linear strand or sequence of deoxyribonucleotide residues, which can anneal by forming hydrogen bonds with another strand having a sequence that is complementary to that of the other and assume a double helical structure. As set forth in the previous Office action, neither strand of the promoter regions of the genes encoding brachyury, α4-integrin, follistatin, and E-cadherin appears to comprise a

polynucleotide sequence comprising the sequence "CACCT-N-CACCT", where N is any number of intervening nucleotides. Accordingly, it has been submitted that the claimed method cannot be practiced, since a nucleic acid sequence comprising the sequence "CACCT-N-CACCT" cannot "originate" from a polynucleotide sequence of the promoter regions of these genes. A sequence, such as the sequence "CACCT-N-CACCT", which *not* originally present in a given polynucleotide sequence, cannot "originate" from that polynucleotide sequence.

At page 12 and 13 of the amendment filed June14, 2004, Applicant has traversed this ground of rejection. Referring to the disclosure at page 5 (paragraph [0010]), Applicant has argued that the specification teaches that the recited promoter regions all contain the sequence "CACCT-N-CACCT".

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Although the specification discloses, for example, at page 5 (paragraph [0010]) that the promoter regions of genes encoding brachyury, α4-integrin, follistatin, and E-cadherin "are bipartite elements of composed of one CACCT sequence (SEQ ID NO:1) and one CACCTG sequence (SEQ ID NO:2)", it is believed that the disclosure should not be construed as teaching that a single *polynucleotide sequence* of these promoter regions comprises both "CACCT" and "CACCTG". Rather, it is believed that the disclosure should be construed as teaching that the polynucleotide sequences of the recited promoter regions comprise one copy of "CACCT" and one copy of its complement, "AGGTG". For example, at page 4 (paragraph [0008]), the specification teaches that Giroldi et al. (*Biochem. Biophys. Res. Commun.* **18**: 453-458, 1997), which is identified as reference 56 by the specification, teaches that the promoter region of a gene encoding E-cadherin comprises "two E-boxes (CANNTG)". In fact, Giroldi et al. teaches that the promoter region of the gene comprises two E-boxes, but the polynucleotide sequence of this region disclosed therein comprises the sequence "**AGGTG**-N-CACCT" (emboldened for emphasis), wherein "N" is a sequence of 44 nucleotides, which differs from a polynucleotide sequence comprising "CACCT-N-

CACCT"; see, e.g., page 456, Figure 3, of Giroldi et al. Furthermore, Sekido et al. (*Mol. Cell. Biol.* **14**: 5692-5700, 1994), to which the specification refers to as reference 30, teaches the promoter of the *Brachyury* gene comprises a polynucleotide sequence comprising the sequence "CACCT**AGGTG**" (emboldened for emphasis), which also differs from a polynucleotide sequence comprising "CACCT-N-CACCT"; see, e.g., page 5695, Figure 2, of Sekido et al. At page 35 (paragraph [0091]), the specification teaches that the promoter of the gene encoding α4-integrin (denoted as "α4I-WT") comprises the sequence "CACCT-N-**AGGTG**" (emboldened for emphasis), which again differs from a polynucleotide sequence comprising "CACCT-N-CACCT".

Accordingly, contrary to Applicant's assertion, the specification does not appear to teach that the promoter regions of the genes encoding brachyury, α4-integrin, follistatin, or E-cadherin contain the sequence "CACCT-N-CACCT", since, instead, the specification teaches the promoters of the genes comprise DNA strands having a polynucleotide sequence comprising the sequences "CACCT**AGGTG**", "CACCT-N-**AGGTG**", or "**AGGTG**-N-CACCT".

The preponderance of factual evidence of record supports the position that, because a nucleic acid molecule comprising the sequence "CACCT-N-CACCT" cannot "originate" from the promoter regions of the genes encoding brachyury, α4-integrin, follistatin, or E-cadherin, the invention, as claimed, cannot be practiced. Again, a sequence, such as the sequence "CACCT-N-CACCT", cannot "originate" from a polynucleotide sequence, if it is *not* originally present within that polynucleotide sequence.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 2-5 and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-5 and 18-20 are indefinite because claims 2, 18, and 19 do not recite an active process step that clearly relates back to the objective recited in the preamble of the claims. Moreover, while the preambles of claims 2, 18, and 19 indicate that the invention can be used to identify transcription factors, none of the steps recited in the body of the claims describe the means by which transcription factors are identified in practicing the invention, as the only active step is the provision of a cell having a nucleic acid of the recited structure capable for use as bait. Although the nucleic acid molecule of which the cell is comprised, or perhaps the cell can be used as "bait", the use of such as bait is not related by any step recited in the body of the claim to the identification of transcription factors. Furthermore, although claim 20 further recites an active step of performing a specificity test to isolate the transcription factor, but this step also fails to clearly relate back to the objective recited in the preamble of claim 19, which is to *identify*, as opposed to isolate, a transcription factor. Absent a process step that clearly relates back to the objective stated in the preamble, the metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained.

In addition, for the reasons explained below, since the preambles of claims 2, 18, and 19 do not appear to recite essential structure or steps or be "necessary to give life, meaning and vitality" to the claims, the preambles appear to be recitations of the purpose or intended use of the invention, which are not claim limitations. However, if the preamble were considered a claim limitation, it is duly noted that the phrase "such as", which is recited in the preambles of claims 2, 18, and 19, would render those claims indefinite because it would be unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). More particularly, those claims would be indefinite because it would be unclear whether the transcription factors identified are limited to activators and repressors, or might include ancillary transcription factors, which do not have activating or repressing activity per se, but rather function as, e.g., assembly proteins that recruit other proteins having activating or repressing activity to the promoter.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 2-4 and 18-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Sekido et al. (*Genes to Cells* **2**: 771-783, 1997) (of record).

Claim 2 recites only one positive process step, namely the provision of a cell having a recited nucleic acid sequence as bait, which does not clearly relate back to the preamble of the claim reciting, "of identifying transcription factors such as activators and/or repressors". Since the preamble does not therefore appear to recite essential structure or steps or be "necessary to give life, meaning and vitality" to the claim, the preamble of claim 2 appears to be a recitation of the purpose or intended use of the invention, which is not a claim limitation. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). *Kropa v. Robie,* 187 F.2d 150, 152, 88 USPQ 478, 480-81 (CCPA 1951). See MPEP § 2111.02. Therefore, claim 2 is drawn to a process comprising providing cells with a nucleic acid sequence comprising two copies of the sequence "CACCT" separated by any number of nucleotides as bait.

Claim 3 recites, "wherein the transcription factor comprises separated clusters of zinc fingers", and so further modifies the purpose or intended use of the invention without reciting further essential structure or steps "necessary to give life, meaning and vitality" to the process according to claim 2. Claim 3 is drawn to a process comprising providing cells with a nucleic acid sequence comprising two copies of the sequence "CACCT" separated by any number of nucleotides as bait.

Claim 4 further limits the nucleic acid sequence of which the provided cell is comprised, but do not recite any additional positive process steps, and so again lack a step that clearly relates back to the preamble of claim 2. Claim 4 is drawn to a process

comprising providing cells with a nucleic acid sequence comprising two copies of the sequence "CACCT" separated by any number of nucleotides as bait, wherein said nucleic acid sequence originates from a promoter region.

Similar to claim 2, claims 18 and 19 also recite only one positive process step, namely the provision of a cell having a recited nucleic acid sequence as bait, which does not clearly relate back to the preamble of the claim reciting, "of identifying transcription factors such as activators and/or repressors". Claims 18 and 19 additionally recite, "as bait *for* the screening of a library encoding potential transcription factors" (italicized for emphasis), but this recitation of intended use for the nucleic acid sequence of which the cell is comprised, or the perhaps the cell, is not related back by the claim to the purpose or intended use of the invention, as recited in the preamble of those claims. Therefore, neither the preamble of claims 18 and 19, nor the recitations of intended use for the nucleic acid sequence of which the cell is comprised, or the perhaps the cell, in the body of those claims, appear to recite essential structure or steps "necessary to give life, meaning and vitality" to the claims, and accordingly do not limit the claims. Therefore, claims 18 and 19 are drawn to a process comprising providing cells with a nucleic acid sequence comprising two copies of the sequence "CACCT" separated by any number of nucleotides as bait.

Claim 20 is drawn to the process of claim 19 further comprising a specificity test. Although claim 20 recites, "performing a specificity test *to* isolate said transcription factors" (italicized for emphasis), merely measuring a specificity cannot achieve the isolation of a transcription factor and moreover the recitation of intended use for the performance of a specificity test is not related back by the claim to the purpose or intended use of the invention, as recited in the preamble of claim 19. Therefore, claim 20 is drawn to the process of claim 19 further comprising performing a specificity test.

Although the specification does not expressly define "a specificity test", the disclosure at pages 39 and 40 (paragraph [0103]), for example, implies the test can include an analysis and comparison of the DNA binding specificities of a transcription factor and mutational variants thereof, or alternatively an analysis and comparison of the DNA binding specificities of a transcription factor for an element of a promoter, and

mutational variants thereof, to which the transcription factor normally binds, as measured indirectly using a reporter gene construct, such as that described.

Sekido et al. teaches a process comprising providing a cell having multiple copies of a nucleotide sequence of a promoter region of a gene encoding a lens cell protein; see entire document (particularly page 775, Figure 3 and its legend, and page 781, column 2). The promoter region, which is designated "HN", comprises the sequence "CACCT", which is flanked on either end by additional sequences; see, e.g., page 775, Figure 3. Therefore, the cell provided by Sekido et al. comprises a nucleic acid molecule comprising more than one copy of the sequence "CACCT-N-CACCT", where "N" is a finite number of nucleotides separating each copy of the sequence "CACCT". Sekido et al. teaches the disclosed process identifies the transcription factor δEF1 as binding to the sequence "CACCT"; see, e.g., page 775, Figure 3. Sekido et al. teaches the transcription factor δEF1 comprises separated clusters of zinc fingers; see, e.g., the abstract. Because Sekido et al. teaches that the transcription factor δEF1 represses the transcription of a reporter gene to which the nucleic acid molecule comprising multiple copies of the promoter region comprising the sequence "CACCT" is operably adjoined, Sekido et al. demonstrates that δEF1 binds specifically to the sequence to regulate its activity in the cell; see, e.g., page 775, Figure 3. Sekido et al. teaches testing the DNA binding specificity of δEF1 using a naturally occurring promoter region and mutational variants thereof, or alternatively using the naturally occurring transcription factor and mutational variants thereof, to define the characteristics of the interactions between the protein and the polynucleotide sequence to which it binds; see, e.g., page 775, Figure 3.

Each of claims 2-4 and 18-19 recite a single positive process step, which the prior art teaches; therefore, absent a showing of any difference, the process of the prior art is deemed the same as the claimed process.

According to claim 20, the specificity test is performed "to isolate said transcription factors". As explained above, this recitation is considered the purpose or intended use of performing a specificity test, but does not serve to distinguish the

process of the prior art from the claimed invention, provided the process of the prior art could be used to isolate a transcription factor. Since defining the binding characteristics of the transcription factor by the testing described by Sekido et al. could be used in a process of isolating the transcription factor, absent a showing of any difference, the process of Sekido et al. is deemed the same as the process of claim 20.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 2-4 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mak et al, (*DNA Cell Biol.* **15**: 1-8, 1996) (of record) in view of Sekido et al. (*Genes Cells.* **2**: 771-783, 1997) (of record) for essentially the reason set forth in section 24 of the Office action mailed March 12, 2004.

Because the *disclosed* invention is a method for screening a cDNA library to isolate a cDNA encoding a transcription factor that binds to and regulates the transcription activity of a promoter region comprising a particular polynucleotide sequence (e.g., CACCT-N-CACCT), here, although not necessary, the preambles of claims 2, 4, 18, and 19 have been considered to imply that the claimed processes comprise positive steps, which are not expressly recited in the bodies of the claims, but which would be understood by the artisan of ordinarily skilled artisan at the time the invention was made to be necessary, if the objective of the performing the claimed process, as recited in the preambles, is to be met.

Thus, claims 2-4 and 18-20 are drawn to a process for identifying transcription factors, including activators and repressors, comprising providing cells having a nucleic acid molecule comprising a nucleotide sequence comprising the sequence "CACCT-N-

CACCT", wherein "N" can be any number of nucleotides. According to the claims 2, 18, and 19, the nucleic acid molecule of which the claim is comprised is used as bait to screen a library encoding potential transcription factors. According to the claim 3, the transcription factor identified by the process comprises separated clusters of zinc fingers. According to claim 4, the nucleotide sequence used as bait in the process originates from a promoter region. According to claim 20, the process further comprises performing a specificity test, which can be used to isolate a cDNA molecule identified as encoding a transcription factor.

Although the specification does not expressly define "a specificity test", the disclosure at pages 39 and 40 (paragraph [0103]), for example, implies the test can include an analysis and comparison of the DNA binding specificities of a transcription factor and mutational variants thereof, or alternatively an analysis and comparison of the DNA binding specificities of a transcription factor for an element of a promoter, and mutational variants thereof, to which the transcription factor normally binds, as measured indirectly using a reporter gene construct, such as that described.

Mak et al. teaches a method by which mammalian cDNA libraries can be screened to isolate cDNA molecules encoding novel transcription factors that interact with E-box sites; see entire document (particularly, page 7, column 2). Mak et al. discloses the E-box site has the consensus sequence "CANNTG", wherein "N" is any deoxyribonucleotide (i.e., A, T, C, or G); see, e.g., page 1, column 1. The method of Mak et al. utilizes an E-box *HIS3* reporter, which is an expression plasmid comprising a promoter region comprising multiple E-box sites comprising the sequence "CANNTG", wherein "N" is any deoxyribonucleotide, which is operably adjoined to the *HIS3* reporter gene; see, e.g., page 3, Figure 1. Mak et al. teaches the E boxes of the promoter region act as "bait" in screening the cDNA library to identify the transcription factors that bind those sites; see, e.g. page 7, column 2. Mak et al. demonstrates that the process can be used to identify and isolate a cDNA molecule encoding a "bHLH" transcription factor, but also suggests the process can be used to identify other types of transcription factors that functionally interact with E-box sites; see, e.g. page 7, column 2.

Although Mak et al. teaches a promoter region comprising multiple E boxes having a consensus sequence of "CANNTG" (wherein "N" can be A, T, C, or G), in which each copy of the E box is separated by a spacer sequence of a finite number of nucleotides, can be used as bait in the screening process, Mak et al. does not expressly teach the E-box site to which the transcription factors can bind can comprise the sequence "CACCT" (claims 2-5 and 18-20). Furthermore, although Mak et al. demonstrates that the process can be used to identify and isolate a cDNA molecule encoding a "bHLH" transcription factor, Mak et al. does not expressly teach the disclosed process can be used to identify transcription factors comprising separated clusters of zinc fingers (claim 3).

Sekido et al. teaches that which is set forth in the rejection of claims 2-4 and 18-20 under 35 USC § 102(b) above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the method of Mak et al. using the promoter region disclosed by Sekido et al. comprising a polynucleotide sequence comprising multiple copies of the sequence "CACCT" separated by a spacer sequence of a finite number of nucleotides as bait to screen a cDNA library to identify novel transcription factors that bind the promoter region's polynucleotide sequence because Mak et al. teaches a process that can be used to screen a cDNA library to identify and isolate cDNA molecules encoding novel transcription factors comprising providing a cell comprising a reporter gene construct containing an operably adjoined promoter region comprising multiple copies of an E box, which is used to as bait in the process, and Sekido et al. teaches a promoter region comprising a polynucleotide sequence comprising multiple E-box sites having the sequence "CACCT" to which transcription factors, including activators and repressors, such as δEF1 comprising separated clusters of zinc fingers, bind, which can be used to identify such transcription factors. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to identify and isolate cDNA molecules encoding novel transcription factors, which bind to the polynucleotide sequence disclosed by Sekido et al. to regulate the transcription of the

gene encoding δ1-crystallin. One ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of success in doing so because Mak et al. teaches the process is designed to identify DNA-binding proteins, more particularly transcription factors that functionally interact with E-box sites, such as those disclosed by Sekido et al., and although Mak et al. exemplifies the use of the process to identify basic helix-loop-helix (bHLH) transcription factors, the ordinarily skilled artisan would have appreciated that the process can be generally applied to identifying any transcription factor, including a zinc finger transcription factor, such as δEF1, that binds E-box sites contained within a promoter and is capable of causing activation or repression of the transcription activity of the promoter upon its binding.

At pages 13-15 of the amendment filed June 14, 2003, Applicant has traversed this ground of rejection. Briefly, Applicant has argued that Mak et al. merely teaches a process for looking for protein-DNA interactions using a candidate protein fused to a GAL4 transcription activation domain, as opposed to screening a library for potential transcription factors. Furthermore, Applicant has argued that Sekido et al. does not teach a promoter region comprising two copies of the sequence "CACCT" separated by a spacer sequence of a finite number of nucleotides ranging from 0 to at least 400.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

In response to Applicant's argument that Mak et al. merely teaches a process for looking for protein-DNA interactions using a candidate protein fused to a GAL4 transcription activation domain, as opposed to screening a library for potential transcription factors, Applicant is directed, for example, to the abstract, which states, "[u]sing this experimental system, we also demonstrate that mammalian cDNA libraries can be screened successfully for cDNA encoding novel bHLH proteins that interact with E-box targets". At the time the invention was made, the ordinarily skilled artisan would have immediately appreciated that the "yeast one-hybrid system" described by Mak et

al. can be used to screen cDNA libraries to identify and isolate cDNA molecules encoding transcription factors that bind to the E-box sites within the promoter region of the *HIS3* reporter gene construct to regulate the transcription of the reporter gene in a cell co-expressing cDNA molecules encoding such a transcription factor.

In response to Applicant's argument that Sekido et al. does not teach a promoter region comprising two copies of the sequence "CACCT" separated by a spacer sequence of a finite number of nucleotides ranging from 0 to at least 400, Applicant is directed to page 757, Figure 3 and the legend thereof, and page 781, column 2. Sekido et al. teaches a luciferase report gene construct comprising a promoter region comprising *eight* copies of the "HN fragment", which comprises the sequence "CACCT". Sekido et al. teaches cells were co-transfected with a reporter plasmid comprising this construct and an expression plasmid comprising a polynucleotide sequence encoding the transcription factor δEF1 or variants thereof. Sekido et al. teaches the level of transcription of the luciferase reporter gene activity was measured indirectly by measuring the luciferase activity contained in the transfected cells. At the time the invention was made, the ordinarily skilled artisan would have immediately appreciated that the transcription assay described by Sekido et al. can be used to identify a cDNA molecule encoding a transcription factor that binds to the E boxes within the promoter region of the luciferase reporter gene construct to regulate the transcription of the reporter gene in a cell co-expressing such a cDNA molecule.

Finally, in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
September 1, 2004

Notice to Comply	Application No.	Applicant(s)	
	10/028,396	HUYLEBROECK ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct the deficiiency, Applicant must submit substitute copies of the sequence listing together with the statement, as indicated below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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